兒童骨髓移植概觀

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兒童骨髓移植的歷史

利用骨髓治療血病的概念早於1900年經已存在。當時的病人被餵服骨髓，但效果並不理想，而這項技術亦漸漸被人淡忘。第二次世界大戰後，這項治療因核武及核電的發展而再次被醫學界重視。

早期透過血管將骨髓移植到人體內的成敗參半，大多數移植都被排斥，只有少數白血病人的病情獲得輕微改善。其他病人均有出疹、肚瀉、黃疸等可致命的症狀，醫學界對骨髓移植研究的熱情亦因此而於六十年代開始冷卻。

當時已發表有關移植組織的排斥和組織(人類白血球抗原，簡稱HLA) 配合的遺傳學，自此醫生可以替病人找尋及挑選出最合適的骨髓捐贈者。 第一次成功的骨髓移植個案始於1968年，一位天生缺乏完整免疫系統的嬰兒成功接受親兄弟的骨髓移植，並於35 年後仍然保持健康。之後，有更多類似的成功個案，而病者都是患有再生障礙性貧血及急性白血病。至1986年，全球已有超過200間移植中心，每年進行多達5,000宗的移植手術。

與此同時，醫學界發現有製造血球細胞功能的幹細胞可以隨意活動於骨髓及血液之間，這情況在化療後的康復期最為明顯。此外，向病者輸入一種叫集落刺激因素(G-CSF)的蛋白質，有助增加幹細胞的活動。1990年中期，很多移植中心除了使用骨髓外，還採用從外周血收集的血幹細胞。有的甚至以幹細胞取代了骨髓，這個程序叫外周血造血幹細胞移植。

胎盤血又稱臍帶血，是最後被發現跟骨髓一樣，擁有大量的幹細胞。1988年，法國研究人員成功為一位Fanconi 氏貧血病童移植從他胞弟出生時採集到的臍帶血。自此，患有白血病、嚴重再生障礙性貧血或其他血病的病童，得以成功接受臍帶血移植。由於臍帶血的幹細胞數目不多， 因此只適用於兒童或身材較細小的成人。目前醫學界正在研究能否擴大臍帶血幹細胞的數目，讓更多成年人可以受惠。

很多需要接受骨髓移植的病人，都不能從親屬當中找到合適的骨髓。1973 年，第一宗非血緣骨髓移植在紐約完成。這次移植成功導致世界各地紛紛成立骨髓捐贈者登記處，美國更於1986 年成立全國骨髓捐贈計劃。直至現在，全球已儲存了超過七百萬自願捐髓者的資料，並有超過20 間臍帶血庫正在收集和保存初生嬰兒的臍帶血。國際之間還發展出相互合作的機制，以促進辨證、測試及獲得所需幹細胞作移植用途。

幹細胞移植的類型

骨髓是骨骼中的海綿組織，內含幹細胞。幹細胞可以製造血液中各種具有不同功能的血液細胞：減低感染的白血球、將氧氣運往身體各組織的紅血球和控制出血現象的血小板。

倘若幹細胞受疾病影響，骨髓不能正常運作，將會產生過多不正常或未成熟的血細胞(如地中海貧血和白血病) ，又或產生過少血細胞(如再生障礙性貧血)。當診斷出這種情況時，以健康捐髓者的幹細胞替換病人的骨髓，進行異基因造血幹細胞移植或可治愈。幹細胞移植亦是治療實體腫瘤的方法之一。為了讓病人接受較高劑量的化療以去除腫瘤，病人原有的幹細胞會首先被提取及冷藏，待完成化療後再次輸入已儲存的幹細胞以作補充。這種以病人本身健康的骨髓或血幹細胞移植的治療方法叫自體幹細胞移植。

幹細胞移植過程

進行移植前，病人要先接受高劑量的化療、或化療加上電療，把不正常的骨髓完全清除。同時，病人的免疫系統亦要先被去除以防止排斥。這個通常為期五至十天的療程叫準備性或條件營造療程。

提取幹細胞的程序會因應骨髓移植所需細胞而有所分別。捐髓者先接受全身麻醉，醫生會在手術室使用針筒從捐髓者的盤骨刺皮抽取骨髓。由於每一下骨刺都

佩殷(右)是全港首位接受骨髓移植的病童。(手術於1991 年2 月在CCC 完成)

Gloria (right) is the first child patient who received bone marrow transplant in Hong Kong. The ransplant was performed at the CCC in February, 1991.

Overview of Pediatric Bone Marrow Transplantation

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History of Pediatric Bone Marrow Transplant

The idea of using bone marrow to treat blood disease is not new. In the early 1900, patients were given marrow orally. Obviously this did not meet with success and interest faded. After the Second World War, this treatment strategy was re-evaluated due to the development of nuclear weapon and generators.

Early attempts to transplant bone marrow into humans via blood vessels were met with mixed success. While a few leukemia patients had transient improvement of their disease, most transplants were rejected. Other patients developed a clinical syndrome of skin rash, diarrhea, and jaundice, which was mostly fatal. The enthusiasm waned in the 60's.

Around this time, the genetics of graft rejection and tissue (called HLA) matching was described. For the first time, physicians were able to match and select the most suitable marrow donor for the patient. The first successful bone marrow transplant of the modern era was performed in 1968, when an infant born without an intact immune system received a transplant from a sibling. This patient remains healthy 35 years later. Similar success was soon reported for patients with severe aplastic anemia and acute leukemia. By 1986, more than 200 transplant centers worldwide were performing 5,000 transplants annually.

Around this time, it was discovered that stem cells (which produces subsequent generations of blood-forming cells) move freely between the bone marrow and the blood stream. This exodus of stem cells into the circulation is most evident during the recovery phase after chemotherapy. It can be also enhanced by the administration of proteins called colony-stimulating factors (G-CSF). By the middle of the 1990's, many transplant centers were using stem cells collected from peripheral blood instead of, or in addition to, bone marrow. Such a procedure is called peripheral blood stem cell transplantation.

'The latest player in the field is placental blood. Like bone marrow, blood collected from the placenta (also known as umbilical cord blood) is rich in stem cells. In 1988, researchers in France transplanted placental blood collected from a newborn child to the baby's sibling — a child with Fanconi anemia. Since then successful cord blood transplants have performed on children with leukemia, severe aplastic anemia, and a number of other blood disorders. Due to the small number of stem cells in a placental blood collection, cord blood transplantation is currently only a suitable option only for children and, possibly, small adults. Research is underway to determine if cord blood cells can be expanded so that more adults can benefit from this therapy.

The majority of patients who could have benefited from a transplant do not have a brother or sister with matching marrow type. In 1973, the first unrelated marrow donor (matched for HLA tissue type) transplant was performed in New York. The success of this procedure led to the establishment of marrow donor registries around the world. In 1986, the National Marrow Donor Program in the US was created. Currently there is information on over 7 millions volunteer donors worldwide. Similarly over 20 umbilical cord blood banks are collecting and preserving placental blood from newborn infants. There is international cooperation to facilitate the identification, testing, and procurement of stem cells to be used for transplantation.

Types of Stem Cell Transplant

The bone marrow is a spongy tissue found inside bones. It contains stem cells, which divide and generate different kinds of blood cells in the circulation. The white blood cells fight infection; the red blood cells carry oxygen to body tissues; and the platelets control bleeding.

Diseases affecting the stem cells result in bone marrow malfunctioning: either by producing too many defective / immature blood cells (e.g. thalassemia and leukemia), or too few blood cells (apalstic anemia). When these conditions are diagnosed, replacement of the patient's marrow with stem cells from a healthy donor may lead to a cure. This type of transplant is called an allogeneic stem cell transplant. A stem cell transplant may also be part of

只能提取小量骨髓，所以醫生要在多個皮刺的部位提取足夠的骨髓。所提取的骨髓經過濾後，會即時灌輸入病人體內。若使用外周血幹細胞，捐髓者會接受三至五天的集落刺激因素，讓幹細胞從骨髓移動到血液中。醫生會使用特殊的針筒，從捐髓者手臂或腹股溝的大動脈把血液分流，再由一部由電腦操控的細胞分隔器把幹細胞抽出，而剩餘的血細胞則會回流到捐髓者體內。

骨髓移植通常於條件營造療程完成後的一至三天內進行。病人會透過導管輸入幹細胞，情況跟接受輸血相似，整個過程需要三十分鐘至兩小時。

骨髓移植的成功率

家長最常問的問題是：「移植中心醫治病童的成功率有多大？」除非能正確地理解移植中心所提供的數據，否則單談成功率是沒有意義的。

幹細胞移植成功與否有賴多個因素，其中最關鍵的是病人進行手術時的病情。病人的白血病若在手術前並未受到傳統化療的控制，即使進行幹細胞移植亦很難治愈，並且復發的機會亦較大。若病人的病情沒有好轉跡象，移植不但未能改善病情，病者更不適宜進行移植手術。還有，病人的健康狀況也是手術成功的重要因素，病人於條件營造療程後會較易受到疾病感染、器官功能減弱和身體變得虛弱，患上併發症的機會往往非常高。此外，捐髓者的類別亦會影響移植手術的結果。病人若接受親屬完全相合的幹細胞移植或自體移植，併發症的發病率會較低；而非血緣捐贈者及不全相合幹細胞移植則比較危險。

手術後的併發症

1. 移植物抗宿主疾病 (簡稱排斥)

由於捐髓者的骨髓未能與患者完全相合，當捐髓者的 T 細胞 (白血球的一種) 於受贈者體內識別出與己不同的細胞組織而進行攻擊時，便會引起移植物抗宿主疾病，簡稱排斥。若捐髓者和受贈者的基因構造差異較大，排斥的機會亦會較高。現在，平均有二至七成的骨髓移植病人會出現這個問題。當然，接受不全相合或非血緣幹細胞移植的病發機會也較高。

急性排斥多於移植後的數週內發生。發病初期，病人的面部和手會出現皮膚疹，後來會擴散至身體各部分及引起紅腫，像曬傷一樣出現脫皮及水泡的現象。還有，腸胃會感到不適，產生痙攣、作嘔及腹水等情況。若有黃疸症狀，皮膚及眼睛變黃，表示肝臟受到影響。急性排斥可以是輕微和短暫性的，但亦可足以致命，視乎有多少器官受到影響以及其嚴重性。

慢性排斥通常於移植後的三個月後發病，或從急性排斥演變過來。病人多會出現皮膚問題，如出疹、膚色變異及皮膚繃緊；還可能使病人的眼睛及口腔乾燥潰瘍，或肝臟出現不正常狀況及體重減輕。病人亦可能有皮膚疤痕及攣縮、脫髮、指甲剝落、吞嚥及呼吸困難的問題。

急性及慢性排斥均可用藥物抑制 T 細胞的活動能力，可是診斷及治療均會減弱病人的免疫系統，增加受感染的機會。

2. 感染

病人在整個移植過程中都有可能受到感染。於準備性療程中，高劑量的化療及幅射治療會破壞病人體內的骨髓，大大減少白血球的數量，使身體無法製造抗體。加上人體的前線防禦系統： 皮膚、口腔及腸胃，也受到損朗，差不多每位病人均於移植後一至兩週內出現發燒症狀。若發燒由細菌性感染引起，則大都對抗生素有所反應。不過，有時發燒是因為經過漫長的抗菌療程由真菌引起的。

雖然病人體內的白血球數目通常於兩至四週後復原，但其免疫系統的功能仍未回復，受病毒、原蟲、寄生蟲及桿菌感染的機會仍然很高。在正常情況下，機體防禦需要六至十二個月才能完全恢復其功能，所以病人會因排斥及其治療而延誤了康復時間。

因此，病人接受移植後要謹防受到感染，必須養成良好的洗手習慣及避免跟其他病人接觸。嚴密的病情監控及使用預防性抗生素，均有助控制一些潛伏於病人體內的病毒再次活動。

總結

血液及骨髓移植已被確認為治療兒童癌病、血液及免疫系統失調的方案，現在每年有超過二千名病童接受此治療。移植是一項非常漫長又劇烈的療程，病者需要衡量成功的機會及移植會所帶來短期和長遠的副作用，方可決定是否接受此項治療。

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玉媛 (中) 是第100位在CCC接受移植手術的病童 (1998年1月)
Yuk Wun (Centre) is the 100th child patient who received transplant at the CCC in January, 1998.

the treatment for patients with solid tumor cancers. In these situations, some of the patient's own stem cell can be collected and frozen. This allows a higher dose of chemotherapy to be given to kill the tumors, and the patient can be "rescued" by reinfusion of the previously stored cells. The use of the patient's own, otherwise normal, marrow or blood stem cells for treatment is called autologous stem cell transplantation.

How does Stem Cell Transplant Work?

Prior to transplant, the patient 's diseased bone marrow has to be destroyed. This usually involves the use of a combination of chemotherapy drugs, or by a combination of chemotherapy and irradiation, given in very high doses. At the same time the patient's immune system is also eliminated to prevent rejection. This phase of treatment is called the preparative or conditioning regimen and typically lasts five to ten days.

The procedure to collect stem cells differs according to nature of the cells used for transplantation. Bone marrow is harvested in a hospital operating theatre. The donor is put under general anesthesia and a needle is inserted into the hipbone. Over several skin puncture sites repeated bone punctures are performed. A small amount of bone marrow is extracted each time and the total quantity of marrow is pooled, filtered, and transported to the patient's room for immediate infusion. If peripheral blood stem cells are to be used, the donor will receive three to five days of G-CSF to mobilize stem cells to move out of the bone marrow into the blood stream. A needle or special tubing is placed in a large vein either in the donor's arm or the groin. Blood flows into a computer-control machine called a cell separator, which will remove the stem cells and return the rest of the blood cells back to the donor.

On the day of transplant, usually one to three days after the completion of conditioning, stem cells are passed into the patient through a catheter, much like a transfusion. Typically the infusion takes 30 minutes to two hours to complete.

Success Rate: Is It Worth All the Side Effects?

The question parents most frequently asked is, "What is the success rate of the transplant center in treating my child's disease?" It should be stressed that success rate quoted by centers is meaningless unless it is properly interpreted.

Many factors influence the success of a stem cell transplant. The most important element is the patient's status of disease at the time of transplant. Leukemia that is not under good control by conventional chemotherapy is very difficult to cure by a stem cell transplant. There is a higher chance of leukemia recurrence in these cases. When there is progressive disease a transplant will not help and should not be done. The health condition of the patient is also critical for the success of the transplant. Active infection, poor function of any organ system, and general debilitation are usually associated with a higher complication rate due to the effect of conditioning. Finally the donor type affects the transplant outcome. Autologous and matched sibling donor transplants have a lower complication rate whereas mismatched and unrelated donor transplants are generally more dangerous.

What Complications Should I be Aware of?

1. Graft-Versus-Host Disease (GVHD)

This condition is triggered by the T cells of the donor, which are a type of white blood cells that recognize and attack the body cells of another individual (that of the recipient). The larger the differences in the genetic makeup between donor and recipient, the higher the likelihood of GVHD . On the average 20 to 70% of transplant recipients may develop this problem, and as expected the incidence is higher when stem cells from an unrelated or mismatched donor are used.

The acute form of GVHD usually appears during the first few weeks after engraftment. The earliest sign is often a skin rash on the patient's face and hands. It may spread to other parts of the body into general redness, similar to a sunburn, with peeling and blistering of the skin. The stomach and the bowel may also be affected, causing cramping,

nausea, and watery diarrhea. Jaundice (yellow color of the skin and eyes) is a sign the liver is also involved. Depending on the number of organs affected and their severity, acute GVHD may be mild and transient or it may be severe and life threatening.

The chronic form of GVHD develops several months after the transplant. It may evolve from the acute form or it may present independently. Patients usually experience skin problems such as a dry itchy rash, color changes, and tightness. Dryness or burning of the mouth and eyes, liver abnormalities and weight loss are also common complaints. Less frequently, patients may suffer from skin scarring and contractures, loss of hair and nails, and swallowing and breathing difficulties.

Both acute and chronic GVHD are treated by medications that suppress the overactive T cells. Both the diagnosis and its treatment weaken the patient's immune system, so there is an increased risk of opportunistic infections.

2. Infections

Transplant patients are prone to infections during all phases of the procedure. With high dose chemotherapy and/or radiation during the preparative phase, the bone marrow is destroyed and the white blood cell count becomes very low. Antibody-producing cells are depleted. The skin and the lining of the mouth and intestine, the body's other first line of defense, are also damaged. The patient is almost certain to have fever in the first two weeks after transplant. Most of these episodes are responsive to antibiotics, suggesting the infections are bacterial in origin. Occasionally fungi may be the cause of the fever, especially after prolonged antibiotic treatment.

Even after the white cell count recovers, usually in two to four weeks' time, the function of the patient's immune system remained subnormal. The risk of unusual infections caused by virus, protozoa, parasite and mycobacterium remain significant. It takes 6 to 12 months or more for the body defense to function at 100% efficiency. Recovery is delayed by GVHD and its treatment.

梓軒(左) 是第194 位在CCC 接受移植手術的病童(2003 年7 月)
Kelvin (left) is the 194th child patient who received transplant at the CCC in July, 2003.

Extra precaution is necessary to prevent infection after transplant. Good hand washing and avoiding contact with others who are ill are of paramount importance. Close surveillance and prophylactic antibiotics may also be helpful to manage the reactivation of some viruses dormant in the patient's body.

Summary

Blood and marrow transplantation are now established treatment modality in the management of childhood cancer, blood and immune disorders. Each year over 2,000 children undergo this treatment. It is a lengthy and vigorous procedure. The decision to proceed with a transplant must be weighed between the chances of success against the short- and long-term side effects of transplantation.

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